UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/714,333	11/14/2003	Anastasia Khvorova	DHARMA 0100-US2	6379

23719 7590 07/18/2008

KALOW & SPRINGUT LLP
488 MADISON AVENUE
19TH FLOOR
NEW YORK, NY 10022

EXAMINER	
PITRAK, JENNIFER S	
ART UNIT	**PAPER NUMBER**
1635	
MAIL DATE	**DELIVERY MODE**
07/18/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/714,333	KHVOROVA ET AL.	
	Examiner	Art Unit	
	JENNIFER PITRAK	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 December 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,38-54,57-66,68 and 70-91* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 38-54, 57-66, 68, and 70-91* is/are rejected.

7)☒ Claim(s) *44-51 and 70-77* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *06/04/2008; 05/08/2008; 04/23/2008;03/28/2008; 12/07/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/03/2007 has been entered.

Remarks

Applicants have amended claims 1, 43, 61, 68, and 86. Applicants have cancelled claims 2-37, 55, 56, 67, and 69 and have added new claims 88-91. **Claims 1, 38-54, 57-66, 68, and 70-91 are pending and are under examination**.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Any objections or rejections presented herein are those that are outstanding. Any objections or rejections not repeated herein from a previous action are withdrawn.

Claim Rejections - 35 USC § 102 – Withdrawn

The rejection of claims under 35 USC § 102(a or e) are withdrawn in response to Applicant's amendments and arguments.

Claim Rejections - 35 USC § 103 - New

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 38-54, 57-66, 68, and 70-91 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tuschl, *et al.* (WO02/44321, of record), Elbashir, et al (2002, of record, 09/05/2007 Office Action), and Walton, *et al.* (1999, Biotech. Bioeng., v.65:1-9, abstract only).

The claims are to methods for obtaining an siRNA molecule or for selecting an siRNA sequence comprising applying one or more criteria to sequence content and positioning within the siRNA molecule or sequence. The only concrete and tangible step of the instant claims is the synthesis of an siRNA molecule or sequence having specific sequence requirements. Therefore, siRNAs meeting these requirements are presumed to have been derived by the claimed method steps.

Tuschl *et al.* disclose synthesized siRNA duplex structures targeting luciferase in Figure 11(I), wherein the last siRNA duplex comprises a 20-base-pair duplex region and the following antisense sequence: 5'-UUCGAAGUAUUCCGCGUACGU-3'. This siRNA comprises a

structure wherein the total number of A or U residues in the first five, the first three, the first two, and the first nucleotide positions at the 5' end of the antisense region of the duplex region is higher than that in the last five, the last three, the last two, and the last nucleotide positions of the 3' end of the antisense region. Moreover, the first 5' position of the antisense region has either an A or U nucleotide and the last 3' position of the antisense region has neither an A nor U nucleotide. Additionally, the antisense region includes the presence of U at positions 1 and 17, the absence of A at position 15, the absence of G at position 1, and the absence of C at position 7, and the absence of U at position 9 of the antisense region. This sequence comprises a GC content between about 30% and 52%, and has at least 2 A or U bases at position 1-5 of the antisense sequence. This siRNA duplex also effectively reduces the relative luminescence of the target luciferase gene. Additionally, Tuschl *et al.* describe an siRNA duplex having the following antisense sequence (Figure 13B): 5'-UUUGAAGUAUUCCGCGUACGUG-3'. This sequence comprises a U residue at position 1, includes the absence of C at position 7, the absence of A at position 15, the absence of G at position 1, and has between about 30% and 52% GC content. This siRNA duplex meets multiple criteria for selecting siRNA as set forth in the instant claims. Tuschl, *et al.* selected a target gene (luciferase), identified candidate siRNAs and selected candidate siRNAs, and synthesized the siRNAs (those identified and selected siRNAs shown in Figures 11 and 13, for example). While Tuschl, *et al.* do not formalize their selection criteria, nor use a computer to do so, it is evident that Tuschl applied selection criteria that overlaps significantly such that siRNAs selected by Tuschl would necessarily also have been selected by the instant algorithm. Accordingly, since Tuschl et al. essentially teach the selection steps of the instant criteria as set forth in the algorithm, albeit for different reasons, the criteria of

the algorithm are not novel. Therefore, the only difference between Tuschl et al. and the instant application is the use of a computer to run the selection criteria. This is not considered to impart patentability as explained below.

Elbashir *et al.* (2002) describes rules useful for designing siRNA molecules. In particular, the design process is drawn to target site characteristics and at page 202 of this reference, Elbashir *et al.* discloses a strategy for identifying regions in an mRNA target for designing siRNA (step 2 of Protocol 1). Elbashir, *et al.* indicate in the paragraph spanning pages 201-2, that a more comprehensive evaluation of all the parameters to be considered for siRNA selection remains to be performed and that the rules they presented are to serve as a starting point for further experimentation regarding siRNA selection.

It was well known at the time of filing of the instant application to use computer-run algorithms to predict antisense oligonucleotide sequence target sites, as evidenced by Walton, *et al.* Walton, *et al.* teach a prediction algorithm to identify antisense sequences with the highest predicted target-binding affinity and the authors further indicate that computational prediction of antisense sequences is more cost-efficient and faster than *in vitro* or *in vivo* selection of sequences and can potentially speed the development of useful antisense sequences (abstract).

It would have been obvious to one of skill in the art at the time of the instant application to establish a method for obtaining an siRNA or selecting an siRNA sequence by applying sequence- and position-specific criteria to candidate siRNA sequences for the purpose of optimizing siRNA activity, as taught by Elbashir at al. Tuschl, *et al.* selected siRNAs meeting the instantly claimed sequence- and position-specific criteria for luciferase silencing, which are consistent with the criteria established by Elbashir. One of skill clearly had a reason to examine

these criteria further because Elbashir, *et al.* explicitly suggested that such examination continue from their studies. Furthermore, in the related field of antisense oligonucleotide-based inhibition of gene expression, it was well known to use computerized algorithms to expedite selection of sequences having the most robust inhibition. Like antisense oligonucleotides of earlier, siRNAs demonstrate varying degrees of inhibition depending on the sequence of the small RNA, as seen in Figure 11 of Tuschl, *et al.*, for example. It would have been immediately apparent to one skilled in the art to develop and computerize a prediction algorithm for siRNA sequences because prediction algorithms in the antisense field was well-known, as taught by Walton, *et al.*, and because determination of prediction rules for siRNAs were explicitly suggested by Elbashir, *et al.* One would reasonably expect that such work would yield a method for selecting optimal siRNAs because both Tuschl, *et al.* and Elbashir, *et al.* demonstrated that siRNAs meeting specific determined criteria performed better than siRNAs not meeting such criteria. Finally, since the apparent selection criteria of Tuschl has such significant overlap with the instantly claimed criteria that the same oligos would necessarily be produced, the claimed criteria is broadly stated such that it embraces criteria set forth in the prior art. Accordingly the only difference between the selection criteria of Tuschl and the instant criteria is that the instant criteria is set forth in a computerized algorithm, which is not patentable in view of the art and case law which indicates that computerizing an algorithm does not confer patentability. Thus, the claims would have been *prima facie* obvious over Tuschl, *et al.*, Elbashir, *et al.*, and Walton, *et al.*

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JENNIFER PITRAK whose telephone number is (571)270-3061. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM, EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jennifer Pitrak, PhD
Examiner
Art Unit 1635

/JD Schultz, PhD/
Supervisory Patent Examiner, Art Unit 1635